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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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05/25/2010

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EXAMINER

MINNIFIELD, NITA M

ART UNIT

PAPER NUMBER

1645

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 09/914,454	<b>Applicant(s)</b> GRANDI ET AL.	
	<b>Examiner</b> N. M. Minnifield	<b>Art Unit</b> 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 22 February 2010.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-4,6,8-21,23,24,32-39 and 43-48 is/are pending in the application.
- 4a) Of the above claim(s) 32-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4 6 8-21 23 24 43-48 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                     |                                                                   |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)         | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____                                                         | 6) <input type="checkbox"/> Other: _____                          |

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## DETAILED ACTION

### *Response to Amendment*

1. Applicants' amendment filed February 22, 2010 is acknowledged and has been entered. Claims 5, 7, 22, 25-31 and 40-42 are now pending in the present application. Claims 1-4, 6, 8-21, 23, 24, 32-39 and 43-48 are pending in the instant application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.
2. This application contains claims 32-39 drawn to an invention nonelected with traverse in the reply filed on January 24, 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
3. Claims 1-4, 6, 8-21, 23, 24 and 43-48 are pending in the instant application.
4. The following is a quotation of the first paragraph of 35 U.S.C. 112:  

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
5. Claims 1-4, 6, 8-21, 23, 24 and 43-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition comprising an immunostimulating amount of Neisseria antigen and an immunostimulating amount of an adjuvant (SEQ ID NO: 1 and an emulsion comprising submicron oil droplets and emulsifying agent (CFA)), does not reasonably provide enablement for immunogenic composition comprising an immunostimulating amount of Neisseria antigen and an immunostimulating amount of an adjuvant (oligonucleotide comprising at least one CG motif and an emulsion comprising submicron oil droplets and emulsifying agent). The specification does not enable

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any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims recite “an oligonucleotide comprising at least one CG motif”. The claims do not define the size of the oligonucleotide and only define two of the nucleotides, CG. The claims do not define whether the “at least one CG motif” is methylated or unmethylated.

The state of the art with regard to the CpG oligonucleotides and stimulating a Th-1 immune response is unpredictable. The state of the art teaches that there are a number of specific characteristics of the oligonucleotide, which are critical for its function as an immunostimulatory molecule. For instance, Krieg (BioDrugs 1998, 5:341-346) teaches that synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was only a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by s-methyl-cytosine, then the oligonucleotide lost its immune stimulatory activity (p. 342). The pending claims neither recite that the C or G is unmethylated nor the length of the oligonucleotide. Yamamoto et al 1994 (Antisense Research and Development, 1994, 4:119-122) teaches that “immunostimulatory activity of oligonucleotides 18 bases or more in length was observed and was proportional to the base length, with a maximum at 22-30 bases. On the other hand, the oligonucleotides 16 bases or less in length were not as active even if they possessed the palindromic sequences. These results indicate that the immunostimulatory activity of oligonucleotides with certain palindromic sequences requires an oligonucleotide at least 18 bases long.” (abstract). Agrawal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches that the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (see page 16 "therapeutic potential of CpG DNA" in particular) and that there is a species-dependent selectivity of CpG DNA, and that the optimal CpG DNA sequences for many vertebrate species are not yet known (p. 119). Further, Agrawal et al. teach that "The presence of unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity..." (See p. 114, bottom of second column). Agrawal also teaches that sequences required for CpG related immune stimulation varies from species to species, and indicates, "The optimal motif for recognition by human immune cells is 'GTCGTT or TTCGTT' (p. 115). Thus indicating that an

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oligonucleotide of 6 nucleotides in length can function as an immunostimulatory agent in humans. Hartmann et al. (J. Immunology, 2000; 164:1617-1624) teaches that the oligonucleotide must be protected from nuclease degradation in order to be effective in vivo. Specifically, Hartmann teaches, "To have in vivo clinical utility, ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the non-bridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN." (see p. 1618). Therefore, in order for an oligonucleotide to stimulate an immune response in vivo it must contain an unmethylated CpG motif, be at least 6 nucleotides in length, and be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage.

With respect to linkage modifications, combinations thereof or ribose nucleotides or combinations with deoxynucleotides and complexed or linked to biodegradable carriers; Weiner (J. Leukocyte Biology, 68:456-463, 2000) states that the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood (see page 461). While the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (see Agarwal et al, Molecular Med, Today, 6:72-81, 2000, especially pp 78-80). Further, the state of the art teaches that the phosphorothioate analogs are the most potent in immune stimulation (see Zhao et al (Biochemical Pharmacology, 51:173-182, 1996, page 173 (abstract) and there is no evidence of record that any sequence that is not fully phosphorothiolated provides for immune stimulation in any model.

With regard to an immunostimulating amount of adjuvants, combination of adjuvants, it is noted that the state of the art is unpredictable. Cox et al (Vaccine, 1997, 15/3:248-256) teaches "...detail the ways in which an adjuvant can act and to attempt a classification of adjuvants based on their mode of action. The end benefit can be threefold. Firstly, if the pathogenesis of a disease is known, than an adjuvant which can generate a protective immune response can be selected for vaccine formulation. Alternatively, if the pathogenesis and immunology are not well understood, then adjuvants which can generate a range of different immune responses can be rationally selected for study. Thirdly, this knowledge can be used to combine different effects as

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desired." (p. 248) The purpose of adjuvant combinations is to combine various adjuvant components to achieve the desired mix of immunological responses. The best known combination is Freund's complete adjuvant (FCA) which combines the immunomodulatory properties of *Mycobacterium tuberculosis* (essentially TDM and MDP) along with the short-term depot effect of w/o emulsions." (p. 253) "Selection of the 'best' adjuvant combination requires some knowledge of the chemical nature of the protective immunogen(s) and some idea of the nature of the immune response which is likely to be protective. however, even where knowledge of both these issues is minimal, rational selection of a small number of basic formulations and additives should permit selection of an effective adjuvant system. It is hoped that this review will help in this rational selection." (p. 253) Cox et al teaches that emulsions can be unstable. Further, Edelman et al (Molecular Biotechnology, 2002, 21:129-148) teaches that "Every adjuvant has a complex and often multi-factorial immunological mechanism, usually poorly understood in vivo. Many determinants of adjuvanticity exist, and each adjuvanted vaccine is unique. Adjuvant safety is critical and can enhance, retard, or stop development of an adjuvanted vaccine. The choice of an adjuvant often depends upon expensive experimental trial and error, upon cost, and upon commercial availability. Extensive regulatory and administrative support is required to conduct clinical trials of adjuvanted vaccines. Finally, comparative adjuvant trials where one antigen is formulated with different adjuvants and administered by a common protocol to animals and humans can accelerate vaccine development." (abstract) (see also, Aucouturier et al Vaccine, 2001, 19:2666-2672 and Wuorimaa et al, I. Infectious Diseases, 2001, 184:1211-1215). Aucouturier et al teaches that there are no universal adjuvants and their action is not yet clear and relies on different mechanisms. Then, they must be adapted according to several criteria, like the target species, the antigens, the type of immune response, the route of inoculation or the duration of immunity. All the above considerations for determining the use of one adjuvant are increased when the selection of a combination of immunostimulating adjuvants as instantly claimed. It would require undue experimentation to practice the claimed invention in view of the unpredictability of the length of the immunostimulatory oligonucleotide, the unmethylated CG and the problem associated with identifying a combination adjuvant.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in

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Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The nature of the invention, breadth of the claims, unpredictability of the state of the art and state of the prior art have all been addressed above. With regard to the function of methylated form of CpG and the CpG molecules that do not contain a PS backbone, it is impossible to predict that a Th-1 based immune response in vivo utilizing the broad genus of molecules as claimed. The process of identifying a combination adjuvant is unpredictable. The amount of additional experimentation is deemed to be undue because in order to practice the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broadly claimed CpG-containing oligonucleotides would be used in stimulating a Th-1 based immune response in vivo as well as combination adjuvants. The level of the skill in the art is deemed to be high (PhD level). One skill in the art would be compelled to perform undue experimentation in order to practice the claimed invention because of the large number of variables connected with the use of such nucleic acids. For example, the instant application does not give guidance as to the type of administration, the times or frequencies of administration, or the dosages required to obtain desired effects. In view of the combination of facts-- the high degree of unpredictability recognized in the art, particularly the required characteristics of the immunostimulatory oligonucleotide in order to be an effective in vivo immunostimulatory oligonucleotide as well as combination adjuvants, the breadth of the claims as mentioned above, the limited number of working examples and guidance in the specification, the high degree of skill required, it is

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concluded that the amount of experimentation required to perform the broadly claimed composition is undue.

Applicant's arguments filed February 22, 2010 have been fully considered but they are not persuasive. Applicants have asserted that there is a certain amount of unpredictability in the art of using a combination of adjuvants in a pharmaceutical composition. Applicants have asserted "that there may be unpredictability as to whether an oil in water adjuvant will work to produce a protective immune response to a given bacteria and unpredictability as to whether an oil in water adjuvant will produce a superior protective immune response to a given bacteria when combined with another class of adjuvant, given that the specification show a that three oil-in-water adjuvants produce generally similar levels of protection and one exemplary oil-in- water adjuvant shows a superior protection when combined with an oligonucleotide comprising at least one motif, one of skill in the art would not need to engage in undue experimentation when testing other oil-in-water adjuvants." (Remarks, pp. 2-3) Further, Applicants have asserted that the claims need not recite what is already known in the art, specifically as it relates CG motifs and their function.

However, it is the Examiner's position that the recitation of "oligonucleotide comprising at least one CG motif" is not sufficient to define one of the components of the claims adjuvant composition. The instant claims do not define "the structure of an oligonucleotide that would have such a function. The claim only defines two of the nucleotides for this oligonucleotides. It is noted that there are certain CG motifs that are required for immunostimulation and they differ in humans versus animals. The state of the art requires that there be at least 6 nucleotides; the recitation of two nucleotides in the instant claims does not enable such immunostimulation. The state of the art with regard to the CpG oligonucleotides and stimulating a Th-1 immune response is unpredictable. The state of the art teaches that there are a number of specific characteristics of the oligonucleotide, which are critical for its function as an immunostimulatory molecule. For instance, Krieg (BioDrugs 1998, 5:341-346) teaches that synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was only a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by s-methyl-



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cytosine, then the oligonucleotide lost its immune stimulatory activity (p. 342). The pending claims neither recite that the C or G is unmethylated nor the length of the oligonucleotide. Yamamoto et al 1994 (Antisense Research and Development, 1994, 4:119-122) teaches that "immunostimulatory activity of oligonucleotides 18 bases or more in length was observed and was proportional to the base length, with a maximum at 22-30 bases. On the other hand, the oligonucleotides 16 bases or less in length were not as active even if they possessed the palindromic sequences. These results indicate that the immunostimulatory activity of oligonucleotides with certain palindromic sequences requires an oligonucleotide at least 18 bases long." (abstract). Agrawal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches that the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (see page 16 "therapeutic potential of CpG DNA" in particular) and that there is a species-dependent selectivity of CpG DNA, and that the optimal CpG DNA sequences for many vertebrate species are not yet known (p. 119). Further, Agrawal et al. teach that "The presence of unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity..." (See p. 114, bottom of second column). Agrawal also teaches that sequences required for CpG related immune stimulation varies from species to species, and indicates, "The optimal motif for recognition by human immune cells is 'GTCGTT or TTCGTT" (p. 115). Thus indicating that an oligonucleotide of 6 nucleotides in length can function as an immunostimulatory agent in humans.

The skilled artisan would require a knowledge of those sequences that should be included in any given CG motif prior to practicing the invention. However, the disclosure fails to provide sufficient guidance pertaining to the composition and length of those sequences that produce a synergistic immune response when combined with another adjuvants. The specification has failed to provide any detailed structural guidance pertaining to the structural requirements for any given CG motif. The disclosure fails to provide adequate guidance pertaining to those immune stimulating adjuvants that can reasonably be expected to produce a synergistic immune response when combined with another adjuvant. Vaccine development is an empirical process that requires extensive experimentation to identify suitable combinations of immunogen and adjuvant(s), routes of inoculation, and immunization regimens. The skilled artisan would still

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need to know which combination of CG, adjuvant, and antigen should be employed. The prior art is unpredictable and teaches that many putative CG elements do not function in the manner desired and often fail to facilitate immune responses to the antigen of interest. Moreover, the skilled artisan cannot reasonably predict which combination of adjuvants will have a synergistic effect when employed concomitantly. The effectiveness of any given preparation will depend upon several factors including the antigen, adjuvants, dose, immunization regimen, and site of immunization. Because of the empirical nature of this process, the skilled artisan cannot reasonably predict which combinations of adjuvants will display synergistic effects when administered concomitantly with an antigen. This is not surprising considering the complexity of the immune system. The claims are of considerable breadth and are not fully supported by the disclosure. The broadest claims are not limited to any particular CG oligonucleotide or immune stimulating adjuvant or antigen. Accordingly, the claims literally encompass tens-of- thousands of permutations. However, the disclosure fails to teach which combination(s) of antigen, CpG oligonucleotide, and adjuvant will produce the desired response. Accordingly, when all the aforementioned factors are considered in toto, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

6. The attempt to incorporate subject matter into this application by reference to various patents and references, see pages 6 and 27-33, is ineffective because an incorporation by reference must be set forth in the specification and must: (1) Express a clear intent to incorporate by reference by using the root words “incorporat(e)” and “reference” (e.g., “incorporate by reference”). The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

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Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

7. No claims are allowed.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/N. M. Minnifield/  
Primary Examiner, Art Unit 1645